REMARKS

Claims 1 to 3, 8 to 10 and 14 were amended by including a feature of claim 5 ("corneal epithelial migration promoter").

New claim 19 includes features that were deleted from claim 9 hereinabove.

With respect of Rule 116, entry of the claim amendments and the new claim is respectfully requested, since the claim amendments and the new claim all involve features that were set forth in the claims prior to the final rejection.

The presently claimed invention concerns a corneal epithelial migration promoter comprising a corneal epithelial migration promoter having an effect of activating Rho as an active ingredient and a pharmacological carrier.

The presently claimed invention is also directed to a method of treating a corneal epithelial disorder comprising administering to a patent in need thereof a therapeutically effective amount of a corneal epithelial migration promoter having an effect of activating Rho.

Claims 1 to 18 were rejected under 36 USC 112, first paragraph, for the reasons set forth on page 2 of the previous Office Action of October 8, 2003, as allegedly failing to comply with the written description requirement.

The reasons why the 35 USC 112, first paragraph rejection were maintained are set forth on page 2, line 10 to page 3, line 13 of the October 6, 2004 Office Action.

The 35 USC 112, first paragraph rejection concerns the following terminology that was set forth in the claims prior to the final rejection: "a compound having an effect of activating Rho".

Initially, it is submitted that since claims 9, 10 and 13 recite specific compounds, such claims should not have been included in the 35 USC 112, first paragraph rejection.

All the present claims now recite the following terminology: "a corneal epithelial migration promoter having an effect of activating Rho". It is respectfully submitted that such new, more specific, terminology in the claims serves to avoid the 35 USC 112, first paragraph rejection.

The term "Rho" is discussed on page 2, lines 14 to 22 of the specification as follows:

> "...an Rho family, which is one of subfamilies of low molecular weight GTP-binding protein, is considered to control the actin-microfilament cystoskeleton. The Rho family consists of members such as Rho, Rac and Cdc 42 and acts downstream from extracellular signals such as cell growth factors. Recently, a target protein which is specific for Rho was identified, and regulation mechanisms of cell phenomena are going to be clarified such as a regulation mechanism of the

> cytoskeleton and the adhesion (Experimental Medicine, 16, 1782-1788 (1998)) and a regulation mechanism of cell movement (Experimental Medicine, 16, 2032-2039 (1998))."

It was admitted in the previous Office Action of October 8, 2003 that the specification discloses examples of structures of some compounds within the scope of what is claimed.

Applicants respectfully further rebut the 35 USC 112 rejection on the basis of the following disclosures set forth in the specification:

(a) On page 5, first paragraph of the specification, the following is stated:

> "Compounds having Rho-activating effects in the present invention mean compounds which augment regulation mechanisms of cell phenomena in which Rho participates."

The above excerpt from the specification provides a definition of a compound having "Rho-activating effects". One of ordinary skill in the art would know from such definition a "corneal epithelial migration promoter having an effect of activating Rho".

(b) As disclosed on page 4, lines 4 to 10 of the specification, to study the participation of Rho in the migration mechanism of the corneal epithelium, the present inventors

conducted a pharmacological test regarding the effects of Rho inhibitors on the corneal epithelium. As a result, the inventors discovered that the corneal epithelial migration is almost completely inhibited when Rho is inhibited. See Table 1 at the middle of page 10 of the specification, which is reproduced hereinbelow:

Table 1

	Migration length (μ m)
Control	454
Exoenzyme C3 (2 μ g/ml)	186

(Each datum in the table is an average of six samples.)

Table 1 shows that when the corneal block is cultured in Exoenzyme C3 which is a Rho inhibitor, corneal migration is almost completely inhibited.

From the above-mentioned findings, it is revealed that Rho, which is the low-molecular weight GTP-binding protein, participates in the migration mechanism of the corneal epithelium (see page 6, lines 2 to 3 of the specification).

(c) The inventors conducted pharmacological tests using oleoyl lysophosphatidic acid ("oleoyl LPA"), which is one of the corneal epithelial migration promoters having Rho-activating effects, to confirm that such substances provide excellent

results with respect to promoting corneal epithelial migration. See Table 2 at the top of page 11 of the specification, which is reproduced hereinbelow:

Table 2

	Migration length (μm)
Control	454
Oleoyl LPA (0.02 μM)	528
(0.2 μM)	658
(2 μM)	712

(Each datum in the table is an average of six samples.)

Further, the inventors confirmed that when corneal epithelial migration promoters having Rho-activating effects and Rho inhibitors were used jointly, the corneal epithelial migration was almost completely inhibited as long as Rho was inhibited. See Table 3 at the bottom of page 11 of the specification, which is reproduced hereinbelow:

Table 3

	Migration length (μm)
Control	454
Exoenzyme C3 (2 μg/ml)	
+ Oleoyl LPA (0.02 μM)	185
+ Oleoyl LPA (0.2 μM)	182
+ Oleoyl LPA (2 μM)	198

(Each datum in the table is an average of six samples.)

These results confirm that the corneal epithelial migration-promoting effect is based on the Rho-activating effect (see page 12, lines 2-3 of the specification).

In view of the above, it is respectfully submitted that one of ordinary sill in the art would readily understand from the disclosure of the present specification that corneal epithelial migration promoters have Rho-activating effects.

In summary, the present specification provides a functional characteristic coupled with a disclosed co-relation between function and structure by defining corneal epithelial migration promoters as having a Rho-activating effect as substances "which augment regulation mechanisms of cell phenomena in which Rho participates". The specification goes on to disclose examples of such compounds (see page 5, lines 4 to 12 of the specification).

In view of the above, withdrawal of the 35 USC 112, first paragraph rejection is respectfully requested.

Claims 1 to 18 were rejected under 35 USC 102 as being anticipated by Liliom et al., Am. Phys. Socl, 274, C1065-C1074, 1998, for the reasons set forth in the Office Action of March 27, 2003 (which refers to page 2 of the August 27, 2002 Office Action).

Liliom et al. describe the testing of the growth promotion actions of cells due to cell division of keratocytes. In contrast to Liliom et al., in the present invention, as apparent from the pharmacological tests described in the present specification, migration promotion actions of epithelium due to migration of corneal epithelial cells are tested. Thus, since the growth promotion action of cells due to cell division of keratocytes differs from the migration promotion action of corneal epithelium due to migration of corneal epithelial cells, the difference between present claims and the cited reference is clear because the present claims are directed to only corneal epithelial migration promoters.

In contrast to Liliom et al., the present invention does not relate to corneal disorders involving keratocytes.

Thus all of the disorders recited in applicants' claims 11 to 13 of corneal ulcer, corneal erosion, keratitis and dry eye are symptoms caused by corneal **epithelial** defects.

Although Liliom et al. tested the effect of oleoyl lysophosphatidic acid ("LPA") for promoting proliferation for corneal keratocytes, Liliom et al. did not test for an effect of LPA on corneal **epithelial** cells (see columns 1 and 17 of Liliom et al.).

The presently claimed invention is novel, since Liliom et al. do not teach or suggest an effect of LPA for (i) promoting proliferation for corneal **epithelial** cells and (ii) therapeutic effects on corneal **epithelial** disorders.

The cornea consists mainly of an epithelial layer, a stromal layer and an endothelial layer. The thickness of the epithelial layer is about one tenth as thick as that of the cornea, whereas the thickness of the stromal layer is about nine tenths as thick as that of the cornea. The corneal epithelial layer protects the eyeball from external stimulation as a barrier to shut-off the corneal stromal layer from outside of the eyeball, whereas the corneal stromal layer participates in the maintenance of water in the cornea and greatly affects transparency of the cornea. The corneal epithelial layer has a five- to six-layer structure of corneal epithelial cells, and the cells are changed in a turnover of about one week. On the other hand, the corneal stromal layer has keratocytes, which are mesenchyme cells, scattered in the stromal layer consisting of an extracellular matrix, and it is said that a turnover of the keratocytes takes two to three years. Accordingly, corneal **epithelial** cells are substantially different from keratocytes in structure, function, etc.

Attached to applicants' AMENDMENT UNDER 37 CFR 1.111 dated November 21, 2002 was a copy of Steven E. Wilson et al., Investigative Ophthalmology & Visual Science, July 1993, Vol. 34, No. 8, 2544-2561, which describes on pages 2554 and 2555 that EGF (epidermal growth factor) has effects for promoting the proliferation for all of epithelial cells, keratocytes and endothelial cells of the cornea (see Figs. 8 and 9 of Wilson et al.). On the other hand, it is shown that HGF (hepatocyte growth factor) and KGF (keratocyte growth factor) promote the proliferation of epithelial cells and endothelial cells, but does not promote the proliferation of keratocytes.

Withdrawal of the anticipation rejection in view of Liliom et al. is thus respectfully requested.

It is respectfully submitted that applicants' claimed invention is not anticipated and is not rendered obvious by the reference.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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